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Title: Sonrotoclax monotherapy demonstrates durable efficacy in patients with relapsed/refractory Waldenström macroglobulinemia: 31.5-month follow-up from a phase 1/1b study

Authors: Chan Y. Cheah[1-3], Constantine S. Tam[4], Ramón García-Sanz[5], Sophie Leitch[6], Emma Verner[7,8], Raul Cordoba[9], Mazyar Shadman[10,11], Paolo Ghia[12,13], Francesc Bosch[14], Uwe Hahn[15], Masa Lasica[16], Christopher D'Angelo[17], Binghao Wu[18], Gabriel Man[19], Yiqian Fang[18], Zachary Ison[19], Sheel Patel[19], Remus Vezan[19], and Peter Browett[20]

Affiliations: [1]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [2]Medical School, University of Western Australia, Crawley, WA, Australia; [3]Linear Clinical Research, Nedlands, WA, Australia; [4]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [6]Te Whatu Ora, Health New Zealand, Auckland, Waitemata, New Zealand; [7]Concord Repatriation General Hospital, Concord, NSW, Australia; [8]University of Sydney, Sydney, NSW, Australia; [9]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [10]Fred Hutchinson Cancer Center, Seattle, WA, USA; [11]University of Washington, Seattle, WA, USA; [12]Università Vita-Salute San Raffaele, Milano, Italy; [13]Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy; [14]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Royal Adelaide Hospital, Adelaide, SA, Australia; [16]St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [17]University of Nebraska Medical Center, Omaha, NE, USA; [18]BeOne Medicines, Ltd, Shanghai, China; [19]BeOne Medicines, Ltd, San Carlos, CA, USA; [20]Auckland City Hospital, Grafton, Auckland, New Zealand

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Introduction: Waldenström macroglobulinemia (WM) remains incurable with current therapies. Additional treatment options are needed for patients with relapsed/refractory (R/R) WM whose disease progresses following standard therapies. Although B-cell lymphoma 2 (BCL2) inhibitor treatment has shown antitumor activity in patients with WM, no BCL2 inhibitors are currently approved for this disease. Sonrotoclax is a next-generation BCL2 inhibitor designed to have high target selectivity,

enhanced pharmacologic potency, and an optimized pharmacokinetic profile characterized by a shorter half-life and minimal drug accumulation. These properties may enable deeper target inhibition while mitigating toxicity. Here, we report updated safety and efficacy results in R/R WM with 31.5 months of follow-up from a phase 1/1b trial of sonrotoclax as monotherapy and in combination regimens in patients with B-cell malignancies (NCT04277637).

Methods: Eligible patients with R/R WM (≥1 prior therapy) received sonrotoclax monotherapy at four target doses (80, 160, 320, or 640 mg QD) following a dose ramp-up to mitigate the risk of tumor lysis syndrome (TLS). Therapy continued until progressive disease (PD) or unacceptable toxicity. The primary endpoint was safety assessed according to NCI-CTCAE v5.0, and the secondary endpoint was overall response rate (ORR; minor response [MR] or better per IWWM-6/modified Owen 2013 criteria). TLS was assessed per Howard 2011 criteria.

Results: As of May 18, 2026, 23 patients with R/R WM had been enrolled in four sonrotoclax dose-escalation cohorts (80 mg, n=6; 160 mg, n=8; 320 mg, n=5; 640 mg, n=4). Median age was 69 years (range, 48-87). The median number of prior therapies was three (range, 1-9); 14 patients (61%) had previously received a Bruton tyrosine kinase (BTK) inhibitor (noncovalent, n=2; covalent, n=14); 22 (96%) received prior anti-CD20 therapy; and 13 (57%) received both. Mutations in *CXCR4* and *TP53* were detected in 41% (9/22) and 27% (6/22) of tested patients, respectively. Fifteen patients discontinued treatment: 10 due to PD, four due to treatment-emergent adverse events (TEAEs; multifocal neurological syndrome, COVID-19 pneumonia, hemolysis, and lethargy), and one due to other (clinical progression based on symptoms). Six patients died while on study because of PD (n=4), COVID-19 (n=1), and pneumonia (n=1); no deaths were related to study treatment. The most common any-grade TEAEs (>25%) were COVID-19 (48%), anemia (35%), arthralgia (26%), and diarrhea (26%). Anemia was the most common grade ≥3 TEAE (22%). Across all dose levels, one case of laboratory TLS occurred; no cases of clinical TLS were reported.

Among 23 patients, the ORR, major response rate (MRR), and very good partial response (VGPR) rate were 78%, 61%, and 22%, respectively. In the sonrotoclax 320-

mg cohort (n=5), the ORR and MRR were 100% and 80% (including two VGPRs). Among nine patients whose most recent therapy was a BTK inhibitor, the ORR was 67% (MR, n=1; partial response, n=4; VGPR, n=1). Nine patients with *CXCR4* mutation achieved an ORR of 78%, and all six patients with *TP53* mutation responded to treatment.

Conclusions: Sonrotoclax monotherapy demonstrated durable clinical activity in heavily pretreated R/R WM patients, including those with high-risk features. All patients who received the sonrotoclax recommended phase 2 dose (320 mg) achieved a response. With extended follow-up, sonrotoclax monotherapy was well tolerated and no new safety signals were identified. These results support the continued evaluation of sonrotoclax monotherapy or combination regimens in patients with WM and are consistent with the safety and efficacy profile of sonrotoclax-based regimens across hematologic malignancies. Sonrotoclax is currently being evaluated in patients with R/R WM in a potentially pivotal phase 2 study (NCT05952037).